UNITED STATES PATENT AND TRADEMARK OFFICE

59

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,195	12/03/2003	Carmen V. Pepicelli	HUIP-P02-032	6922

28120 7590 09/20/2005

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,195	PEPICELLI ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 18-21* is/are rejected.

7)☒ Claim(s) *1-4 and 18-21* is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Zachary C. Howard, Art Unit 1646, Technology 1600.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-4 and 18-21, drawn to methods of using ptc therapeutics, in the reply filed 6/27/05 is acknowledged.

The traversal is on the ground(s) that the inventions of Groups I-IX are directed to overlapping subject matter related to methods of using hedgehog therapeutics and ptc therapeutics; searches related to hedgehog therapeutics and ptc therapeutics are co-extensive; and therefore the inventions of Groups I-IX can be examined simultaneously without significant additional burden.

This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof; (B) a separate status in the art when they are classifiable together; or (C) a different field of search. These criteria were met in the restriction requirement in the previous Office Action of 5/23/05. Applicants arguments that the inventions of Groups I-IX are directed to overlapping subject matter, specifically methods using hedgehog therapeutics and methods using ptc therapeutics, is not deemed persuasive. In the statement on page 3 of the 5/23/05 Office Action, the inventions were deemed to have acquired a separate status in the art because of either their different classification, recognized divergent subject matter, and/or the need for non-coextensive search. For example, the methods using hedgehog therapeutics and ptc therapeutics are distinct inventions because they are drawn to different proteins with different sequences and different structures. As defined in the specification, the term "hedgehog therapeutic" (pg 11) refers to various forms of hedgehog polypeptides and peptidomimetics that mimic or inhibit the effects of hedgehog protein, whereas "ptc therapeutic" (pg 12) encompasses peptides, nucleic acids, carbohydrates, small organic molecules, or natural product extracts that activate

or potentiate patched signaling. They thus require separate searches and separate considerations, and support separate patents. Thus, the groups require divergent searches, and to search all inventions of Groups I-IX would be burdensome. For these reasons and those in the 5/23/05 Office Action, the requirement is still deemed proper and is therefore made FINAL.

Claims 5-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/27/05.

Claims 1-4 and 18-21 are under consideration, in so far as they read upon methods using ptc therapeutics.

Specification

The disclosure is objected to because of the following informalities:

1) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the status of referenced application 09/394020 should be updated to reflect that this application is now abandoned.

3) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "REGULATION OF LUNG TISSUE BY PATCHED THERAPEUTIC AND FORMULATIONS AND USES RELATED THERETO".

Appropriate correction is required.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 1R and Figure 2A-2K. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in

the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1-4 are objected to because the claim encompasses non-elected inventions, specifically methods using a hedgehog therapeutic (Groups II-IX of the 5/23/05 Restriction Requirement). Appropriate correction is required.

Claims 1-2 and 18-21 are objected to because (abbreviations (i.e., "ptc")) should be spelled out in all independent claims for clarity.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for modulating the growth state of lung tissue, or for inducing a the formation of lung tissue with Sonic hedgehog, does not reasonably provide enablement for said with other ptc therapeutics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1 and 18 encompass a method for modulating the growth state of lung tissue, or cells derived from lung tissue, comprising ectopically contacting the tissue with a ptc therapeutic that will alter the proliferation of the lung tissue. The term modulating encompasses both induction of proliferation and inhibition of proliferation. The term "ptc therapeutic" as defined (pg 12) encompasses any agent that activates or potentiates patched signaling; or is a hedgehog antagonist (which is defined on pg 11 as inhibiting the activity of a wild-type hedgehog protein). Page 12 further teaches that the ptc therapeutic can be a peptide, a nucleic acid, a carbohydrate, a small organic molecule, or a natural product extract. Pages 5-6 teach examples of ptc therapeutics including small organic molecules which induce hedgehog-mediated patched signal transduction by either binding patched or by altering the localization, binding, enzymatic activity, or expression of an intracellular protein involved in a patched signal pathway; an antisense construct that inhibits expression of a protein in said pathway; or an inhibitor of protein kinase A. Therefore, it is clear from the specification that the term ptc therapeutic includes molecules that will either induce or inhibit the patched pathway.

Claim 2 is drawn to a similar method to claim 1, but limits the method to induction of formation of lung tissue. Claim 3 limits the method of claim 1 to an in vitro culture, and claim 4 limits the method to in vivo administration of the agent to an animal. Claim 19 limits the ptc therapeutic to a small organic molecule which binds patched and derepressed patched-mediated inhibition of mitosis. Claim 20 limits the method of claim 18 to one wherein the ptc therapeutic binds to patched and mimics hedgehog-mediated signal transduction. Claim 21 limits claim 20 to a small organic molecule.

The prior art teaches that the N-terminal fragment of Sonic hedgehog (Shh-N) is capable of stimulating *in vitro* proliferation of lung squamous carcinoma, which are cells derived from lung tissue (see pg 661 of Fujita et al, published 9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665). The prior art also teaches that overexpression of Shh induces proliferation of mouse lung mesenchymal cell *in vivo* (see pg 54 of Bellusci et al, 1997, Development, 124: 53-63; cited as reference CB in the IDS filed 12/3/03). The prior art does not teach other examples of molecules that are encompassed by the term ptc therapeutic that are capable of stimulating *in vitro* or *in vivo* proliferation of lung tissue,

The amount of direction or guidance provided by Applicants regarding the structure or nature of the compounds encompassed by the claimed methods is minimal. The specification teaches that a null mutant of the *Shh* gene leads to improper lung growth and formation (pg 69). The specification (pgs 48-62) outlines general *in vitro* methods for screening compounds to determine whether or not the compounds that have the ability to modulate lung tissue proliferation. The specification does not identify any compounds that actually have the ability to modulate lung tissue proliferation. The specification merely invites the skilled artisan to engage in further undue experimentation to screen compounds *in vitro* in order to determine whether or not they have the ability to modulate lung tissue proliferation.

Furthermore, claims 1, 2, 4 and 18-21 encompass *in vivo* methods of modulating (inducing or inhibiting) lung tissue proliferation with a ptc therapeutic. The relevant art discusses the therapeutic potential of modulators of the Hedgehog-Gli signaling pathway (including patched) (Stecca et al, 2002, Journal of Biology. 1(9):1-4). Stecca discusses the development of a hedgehog agonist that "promotes proliferation and differentiation in a cell-type-specific manner *in vitro*, while *in vivo* it rescues developmental defects of Shh-null mouse embryos." Stecca further teaches "From a therapeutic point of view, the fact that the molecule retains its activity after oral administration is a great advantage and, if its ability to cross the blood-brain and placental barriers occurs in humans, it could be a very valuable therapeutic agent." This teaching of Stecca highlights the need for in vivo confirmation of the effects of a

potential modulator before it can be concluded that it is an in vivo therapeutic. Therefore, even if a compound capable of modulating lung cell proliferation was identified in an in vitro assay, this would not enable one skilled in the art to use the compound to modulate *in vivo* proliferation without further undue experimentation to determine whether or not the compound also works *in vivo*. Furthermore, even if the compound were to have an *in vivo* effect, therapeutic use would require further experimentation to determine the quantity of the ptc therapeutic to be administered, the most effective administration route, and the duration of the treatment. The specification lacks direction/guidance presented in the specification regarding the *in vivo* use of ptc therapeutics and/or working examples directed to the same.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how the method of the present invention could be used to modulate proliferation of lung tissue, or cells derived from, with any ptc therapeutic other than Shh-N. There are no examples of other compounds that modulate proliferation of lung tissue. Thus the specification fails to teach the skilled artisan how to use the method to modulate lung cell proliferation without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

Due to the large quantity of experimentation necessary to identify other ptc therapeutics that could be used in the claimed method, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claims 1-4 and 18-21 are drawn to a method for modulating the growth state of lung tissue, or for inducing the formation of, or the maintenance or functional performance of lung tissue, with an agent, wherein the agent is a ptc therapeutic.

Page 12 teaches that the ptc therapeutic can be a peptide, a nucleic acid, a carbohydrate, a small organic molecule, or a natural product extract. Pages 48-61 teach methods of screening or assaying libraries of compounds in order to identify ptc therapeutics. The specification teaches that Sonic hedgehog protein expression is required for proper lung formation (p 69, lines 1-3). The specification does not teach the identity, or any structural characteristics, of other compounds that will function to modulate the growth state of lung tissue.

Of the potential ptc therapeutics, only Sonic hedgehog is established in the prior art as inducer of lung tissue proliferation (Fujita et al, published 9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665). What is missing from the specification is a disclosure of other specific ptc therapeutics which will modulate the growth state of lung tissue. Without a disclosure of these ptc therapeutics the specification lacks adequate written description to support the scope of the claims, and a meaningful search of methods of use of these compounds cannot be performed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The skilled artisan cannot envision the chemical structure of compound encompassed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only methods comprising Sonic hedgehog, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "small" in claims 19 and 21 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Use of the term "small" renders indefinite the term "organic molecule". The term "small" is not defined in relation to anything, so it is unclear what does or does not constitute a "small" organic molecule. For art purposes, the term will be interpreted to include any organic molecule, such as a protein.

Claim 20 is indefinite because it recites "wherein the ptc therapeutic binds to patched and mimics hedgehog-mediated patched signal transduction". It is unclear how "the ptc therapeutic" which binds to patched can also mimic hedgehog-mediated patched signal transduction. The term "signal transduction" generally refers to a process of transmitting information from one location to another. It is unclear how a compound (a ptc therapeutic) can mimic a process (signal transduction).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4 and 18-21 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Fujita et al, published 9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665.

Claims 1, 2, 3 and 18-21 each encompass an *in vitro* method for inducing lung tissue proliferation or formation with a ptc therapeutic. The definition of the term "*ptc* therapeutic" page 12 includes agents that activate or potentiate patched signaling; therefore, this term encompasses the N-terminal fragment of Sonic hedgehog protein (Shh-N). The term "small organic molecule" in claims 19 and 21 is not defined in the specification and therefore also encompasses Shh-N. Fujita teaches that human Shh-N stimulates proliferation of human lung squamous carcinoma cells (pg 661). Human lung squamous carcinoma cells meet the definition of cells derived from lung tissue. Therefore, this teaching of Fujita clearly anticipates claims 1, 2, 3 and 18-21.

Claim 4 encompass a method for modulating the growth state of lung tissue comprising ectopically contacting the tissue with a ptc therapeutic that is administered to the animal as a therapeutic composition. Fujita teaches, "overexpression of Shh induces a mitogenic effect on mouse lung mesenchymal cells and skin keratinocytes in vivo" (pg 658). Therefore, Fujita clearly anticipates claim 4.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

Bridget C. Bunner

BRIDGET BUNNER
PATENT EXAMINER